STN SEARCH 10/043,787 07/18/2005
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FILE 'HOME' ENTERED AT 11:29:46 ON 18 JUL 2005

=> index bioscience medicine
FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED
COST IN U.S. DOLLARS SINCE FILE TOTAL
ENTRY SESSION
FULL ESTIMATED COST 0.21 0.21

INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, ANTE, AQUALINE, AQUASCI, BIOBUSINESS, BIOCOMMERCE, BIOENG, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CANCERLIT, CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DISSABS, ...' ENTERED AT 11:30:02 ON 18 JUL 2005

77 FILES IN THE FILE LIST IN STNINDEX

Enter SET DETAIL ON to see search term postings or to view
search error messages that display as 0* with SET DETAIL OFF.

=> S (SAHase or adohcyase or (adenosylhomo? (s) hydrolas?) or adenosylhomocysteinase# or (adenosylhomocysteine (s)synthase?))
16 FILE ADISCTI
7 FILE ADISINSIGHT
23 FILE AGRICOLA
19 FILE ANABSTR
2 FILE AQUASCI
18 FILE BIOBUSINESS
1 FILE BIOCOMMERCE
42 FILE BIOENG
599 FILE BIOSIS
20 FILE BIOTECHABS
20 FILE BIOTECHDS
238 FILE BIOTECHNO
83 FILE CABA
144 FILE CANCERLIT
839 FILE CAPLUS
5 FILE CEABA-VTB
1 FILE CEN
27 FILE CONFSCI
2 FILE CROPU
51 FILE DDFB
201 FILE DDFU
328 FILE DGENE
37 FILE DISSABS
51 FILE DRUGB
218 FILE DRUGU
31 FILES SEARCHED...
4 FILE EMBAL
626 FILE EMBASE
183 FILE ESBIOBASE
11* FILE FEDRIP
1 FILE FROSTI
2 FILE FSTA
1510 FILE GENBANK
18 FILE IFIPAT
2 FILE IMSRESEARCH
36 FILE JICST-EPLUS
188 FILE LIFESCI
626 FILE MEDLINE
1 FILE NIOSHTIC
16 FILE NTIS
1 FILE OCEAN
364 FILE PASCAL
7 FILE PHAR
1 FILE PHIN
3 FILE PROMT
7 FILE PROUSDDR

714 FILE SCISEARCH
478 FILE TOXCENTER
190 FILE USPATFULL
13 FILE USPAT2
1 FILE VETB
3 FILE VETU
19 FILE WPIDS
19 FILE WPINDEX
1 FILE IPA
75 FILES SEARCHED...
1 FILE NAPRALERT
4 FILE NLDB

56 FILES HAVE ONE OR MORE ANSWERS, 77 FILES SEARCHED IN STNINDEX

L1 QUE (SAHASE OR ADOHCYASE OR (ADENOSYLHOMO? (S) HYDROLAS?) OR ADENOSYLHOMOC YSTEINASE# OR (ADENOSYLHOMOCYSTEINE (S) SYNTHASE?))

=> d rank
F1 1510 GENBANK
F2 839 CAPLUS
F3 714 SCISEARCH
F4 626 EMBASE
F5 626 MEDLINE
F6 599 BIOSIS
F7 478 TOXCENTER
F8 364 PASCAL
F9 328 DGENE
F10 238 BIOTECHNO
F11 218 DRUGU
F12 201 DDFU
F13 190 USPATFULL
F14 188 LIFESCI
F15 183 ESBIOBASE
F16 144 CANCERLIT
F17 83 CABA
F18 51 DDFB
F19 51 DRUGB
F20 42 BIOENG
F21 37 DISSABS
F22 36 JICST-EPLUS
F23 27 CONFSCI
F24 23 AGRICOLA
F25 20 BIOTECHABS
F26 20 BIOTECHDS
F27 19 ANABSTR
F28 19 WPIDS
F29 19 WPINDEX
F30 18 BIOBUSINESS
F31 18 IFIPAT
F32 16 ADISCTI
F33 16 NTIS
F34 13 USPAT2
F35 11* FEDRIP
F36 7 ADISINSIGHT
F37 7 PHAR
F38 7 PROUSDDR
F39 5 CEABA-VTB
F40 4 EMBAL
F41 4 NLDB
F42 3 PROMT
F43 3 VETU
F44 2 AQUASCI
F45 2 CROPU
F46 2 FSTA
F47 2 IMSRESEARCH
F48 1 BIOCOMMERCE
F49 1 CEN
F50 1 FROSTI
F51 1 NIOSHTIC

F52 1 OCEAN
F53 1 PHIN
F54 1 VETB
F55 1 IPA
F56 1 NAPRALERT
=> file f2-f7, f10, f14-f16
COST IN U.S. DOLLARS SINCE FILE TOTAL
ENTRY SESSION
FULL ESTIMATED COST 5.31 5.52

FILE 'CAPLUS' ENTERED AT 11:35:20 ON 18 JUL 2005
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FILE 'CANCERLIT' ENTERED AT 11:35:20 ON 18 JUL 2005

=> s L1
L2 4635 L1

=> s (mutant# or mutat? or variant? or alter?) (s) l2
8 FILES SEARCHED...
L3 238 (MUTANT# OR MUTAT? OR VARIANT? OR ALTER?) (S) L2

=> S (assay? or test? or measur? or detect? or method?) (s) L3
3 FILES SEARCHED...
5 FILES SEARCHED...
7 FILES SEARCHED...
9 FILES SEARCHED...
L4 50 (ASSAY? OR TEST? OR MEASUR? OR DETECT? OR METHOD?) (S) L3

=> dup rem l4
PROCESSING COMPLETED FOR L4
L5 28 DUP REM L4 (22 DUPLICATES REMOVED)

=> d ibib abs L4 1-28

L4 ANSWER 1 OF 50 CAPLUS COPYRIGHT 2005 ACS on STN ✓
ACCESSION NUMBER: 2003:571242 CAPLUS
DOCUMENT NUMBER: 139:130399
TITLE: ***Methods*** and compositions for ***assaying*** homocysteine for enzymatic analysis of human ***mutant*** S-***adenosylhomocysteine*** ***hydrolase*** and diagnostic application
INVENTOR(S): Yuan, Chong-Sheng
PATENT ASSIGNEE(S): General Atomics, USA

inventor

SOURCE: PCT Int. Appl., 103 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003060478	A2	20030724	WO 2003-US866	20030110
WO 2003060478	A3	20040108		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-43787 A 20020110

AB The present invention relates to compns. and methods for assaying homocysteine (Hcy) and thus related moieties, e.g., S-adenosylhomocysteine (SAH) or adenosine. More particularly, assay methods that employ, mutant SAH hydrolase having binding affinity for Hcy, SAH or adenosine but has attenuated catalytic activity, are provided. The modified enzymes and fusion proteins contg. the modified enzymes are also provided. Pecific mutations include amino acid residue substitution(s) at catalytic site, its binding site for NAD+, NADH, Hcy, SAH or adenosine, or a combination, such as R38E, C53S, L54G, T57G, T57S, E59D, N80G, S83G, Y100T, K121A, D131E, D134E, E155G, T157G, T158Y, T159Y, N181D, N181A, D19OA, N191A, L214A, Y221S, K226A, F235S, I240L, N248A, D263G, G269D, R285D, D292G, H301T, K309R, K322G, R329A, L347F, L347Y, L3471, M351A, H353R, S361G, F362S, Y379S, L386A, K388G, H398A, K401R, K401D, T407S, L409G, S420T, P424A, F425S, P427A, D428G, H429A, Y430T, R431K, R431G, Y432S, Y432A, and Y432F.

L4 ANSWER 2 OF 50 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:31675 CAPLUS
DOCUMENT NUMBER: 134:83111
TITLE: Methods and compositions for assaying analytes
INVENTOR(S): Yuan, Chong-Sheng
PATENT ASSIGNEE(S): General Atomics, USA
SOURCE: PCT Int. Appl., 187 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001002600	A2	20010111	WO 2000-US18057	20000630
WO 2001002600	A3	20020110		
WO 2001002600	C2	20020725		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 6376210	B1	20020423	US 1999-347878	19990706
CA 2377665	AA	20010111	CA 2000-2377665	20000630
GB 2368641	A1	20020508	GB 2002-425	20000630
GB 2368641	B2	20041006		

PRIORITY APPLN. INFO.: US 1999-347878 A 19990706

US 1999-457205 A 19991206
WO 2000-US18057 W 20000630

AB Compns. and methods for assaying analytes, preferably, small mol. analytes are provided. Assay methods employ, in place of antibodies or mols. that bind to target analytes or substrates, modified enzymes, called substrate trapping enzymes. These modified enzymes retain binding affinity or have enhanced binding affinity for a target substrate or analyte, but have attenuated catalytic activity with respect to that substrate or analyte. The modified enzymes are provided. In particular, mutant S-adenosylhomocysteine (SAH) hydrolases, substantially retaining binding affinity or having enhanced binding affinity for homocysteine or S-adenosylhomocysteine but having attenuated catalytic activity, are provided. Conjugates of the modified enzymes and a facilitating agent, such as agents that aid in purifn. or linkage to a solid support are also provided.

L4 ANSWER 3 OF 50 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:607411 CAPLUS
DOCUMENT NUMBER: 113:207411
TITLE: Site-directed mutagenesis of rat liver S-adenosylhomocysteinase. Effect of conversion of aspartic acid 244 to glutamic acid on coenzyme binding
AUTHOR(S): Gomi, Tomoharu; Takata, Yoshimi; Date, Takayasu; Fujioka, Motoji; Aksamit, Robert R.; Backlund, Peter S., Jr.; Cantoni, Giulio L.
CORPORATE SOURCE: Fac. Med., Toyama Med. Pharm. Univ., Sugitani, 930-01, Japan
SOURCE: Journal of Biological Chemistry (1990), 265(27), 16102-7
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Aspartic acid (Asp) 244 that occurs at the putative NAD+-binding site of rat liver S-adenosylhomocysteinase was replaced by glutamic acid by oligonucleotide-directed mutagenesis. The mutant enzyme was purified to homogeneity as judged by SDS-PAGE. Gel permeation chromatog. showed that the purified mutant enzyme was a tetramer as is the wild-type enzyme. In contrast to the wild-type enzyme, which possesses 1 mol of tightly bound NAD+ per mol of enzyme subunit, the mutant enzyme had only 0.05 mol of NAD+ but contained .apprx.0.6 mol each of NADH and adenine per mol of subunit. The ***mutant*** enzyme, after removal of the bound compds. by acid(NH)2SO4 treatment, exhibited S- ***adenosylhomocysteinase*** activity when ***assayed*** in the presence of NAD+. From the appearance of activity as a function of NAD+ concn., the enzyme was shown to bind NAD+ with a Kd of 23.0 .mu.M at 25.degree., a value >280-fold greater than that of the wild-type enzyme. In the presence of a satg. concn. of NAD+, the mutant enzyme showed apparent Km values for substrates similar to those of the wild-type enzyme. Moderate decreases of 8- and 15-fold were obsd. in Vmax values for the synthetic and hydrolytic directions, resp. These results indicate the importance of Asp-244 in binding NAD+, and are consistent with the idea that the region of S-adenosylhomocysteinase from residues 213 to 244 is part of the NAD+-binding site. This region has structural features characteristic of the dinucleotide-binding domains of NAD+- and FAD-binding proteins (Ogawa, H. et al., 1987).

L4 ANSWER 4 OF 50 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 90330385 EMBASE
DOCUMENT NUMBER: 1990330385
TITLE: Site-directed mutagenesis of rat liver S-adenosylhomocysteinase. Effect of conversion of aspartic acid 244 to glutamic acid on coenzyme binding.
AUTHOR: Gomi T.; Takata Y.; Date T.; Fujioka M.; Aksamit R.R.; Backlund Jr. P.S.; Cantoni G.L.
CORPORATE SOURCE: Dept. of Biochemistry, Faculty of Medicine, Toyama Med./Pharma. Univ., 2630 Sugitani,Toyama 930-01, Japan
SOURCE: Journal of Biological Chemistry, (1990) Vol. 265, No. 27, pp. 16102-16107.
ISSN: 0021-9258 CODEN: JBCHA3

COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 911213
Last Updated on STN: 911213

AB Aspartic acid 244 that occurs at the putative NAD+-binding site of rat liver S-adenosylhomocysteinase was replaced by glutamic acid by oligonucleotide-directed mutagenesis. The mutant enzyme was purified to homogeneity as judged by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Gel permeation chromatography showed that the purified mutant enzyme was a tetramer as is the wild-type enzyme. In contrast to the wild-type enzyme, which possesses 1 mol of tightly bound NAD+ per mol of enzyme subunit, the mutant enzyme had only 0.05 mol of NAD+ but contained about 0.6 mol each of NADH and adenine per mol of subunit. The ***mutant*** enzyme, after removal of the bound compounds by acid-ammonium sulfate treatment, exhibited S-***adenosylhomocysteinase*** activity when ***assayed*** in the presence of NAD+. From the appearance of activity as a function of NAD+ concentration, the enzyme was shown to bind NAD+ with a K(d) of 23.0 .mu.M at 25 .degree.C, a value >280-fold greater than that of the wild-type enzyme. In the presence of a saturating concentration of NAD+, the mutant enzyme showed apparent K(m) values for substrates similar to those of the wild-type enzyme. Moderate decreases of 8- and 15-fold were observed in V(max) values for the synthetic and hydrolytic directions, respectively. These results indicate the importance of Asp-244 in binding NAD+, and are consistent with the idea that the region of S-adenosylhomocysteinase from residues 213 to 244 is part of the NAD+ binding site. This region has structural features characteristic of the dinucleotide-binding domains of NAD+- and FAD-binding proteins (Ogawa, H., Gomi, T., Mueckler, M. M., Fujioka, M., Backlund, P. S., Jr., Aksamit, R. R., Unson, C. G., and Cantoni, G. L. (1987) (1978) Proc. Natl. Acad. Sci. U.S.A. 84, 719-723).

L4 ANSWER 5 OF 50 MEDLINE on STN
ACCESSION NUMBER: 90375464 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1975808
TITLE: Site-directed mutagenesis of rat liver S-adenosylhomocysteinase. Effect of conversion of aspartic acid 244 to glutamic acid on coenzyme binding.
AUTHOR: Gomi T; Takata Y; Date T; Fujioka M; Aksamit R R; Backlund P S Jr; Cantoni G L
CORPORATE SOURCE: Department of Biochemistry, Toyama Medical and Pharmaceutical University Faculty of Medicine, Japan.
SOURCE: Journal of biological chemistry, (1990 Sep 25) 265 (27) 16102-7.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199010
ENTRY DATE: Entered STN: 19901122
Last Updated on STN: 19970203
Entered Medline: 19901018

AB Aspartic acid 244 that occurs at the putative NAD(+)-binding site of rat liver S-adenosylhomocysteinase was replaced by glutamic acid by oligonucleotide-directed mutagenesis. The mutant enzyme was purified to homogeneity as judged by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Gel permeation chromatography showed that the purified mutant enzyme was a tetramer as is the wild-type enzyme. In contrast to the wild-type enzyme, which possesses 1 mol of tightly bound NAD+ per mol of enzyme subunit, the mutant enzyme had only 0.05 mol of NAD+ but contained about 0.6 mol each of NADH and adenine per mol of subunit. The ***mutant*** enzyme, after removal of the bound compounds by acid-ammonium sulfate treatment, exhibited S-***adenosylhomocysteinase*** activity when ***assayed*** in the presence of NAD+. From the appearance of activity as a function of NAD+ concentration, the enzyme was shown to bind NAD+ with a Kd of 23.0 microM

at 25 degrees C, a value greater than 280-fold greater than that of the wild-type enzyme. In the presence of a saturating concentration of NAD+, the mutant enzyme showed apparent Km values for substrates similar to those of the wild-type enzyme. Moderate decreases of 8- and 15-fold were observed in Vmax values for the synthetic and hydrolytic directions, respectively. These results indicate the importance of Asp-244 in binding NAD+, and are consistent with the idea that the region of S-adenosylhomocysteinase from residues 213 to 244 is part of the NAD+ binding site. This region has structural features characteristic of the dinucleotide-binding domains of NAD(+)- and FAD-binding proteins (Ogawa, H., Gomi, T., Mueckler, M. M., Fujioka, M., Backlund, P.S., Jr., Aksamit, R.R., Unson, C.G., and Cantoni, G.L. (1987) Proc. Natl. Acad. Sci. U.S.A. 84, 719-723).

L4 ANSWER 6 OF 50 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1990:516429 BIOSIS
DOCUMENT NUMBER: PREV199090133705; BA90:133705
TITLE: SITE-DIRECTED MUTAGENESIS OF RAT LIVER S ADENOSYLHOMOCYSTEINASE EFFECT OF CONVERSION OF ASPARTIC ACID 244 TO GLUTAMIC ACID ON COENZYME BINDING.
AUTHOR(S): GOMI T [Reprint author]; TAKATA Y; DATE T; FUJIOKA M; AKSAMIT R R; BACKLUND P S JR; CANTONI G L
CORPORATE SOURCE: DEP BIOCHEM, TOYAMA MED AND PHARMACEUTICAL UNIV FAC OF MED, 2630 SUGITANI, TOYAMA 930-01, JAPAN
SOURCE: Journal of Biological Chemistry, (1990) Vol. 265, No. 27, pp. 16102-16107.
CODEN: JBCHA3. ISSN: 0021-9258.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 19 Nov 1990
Last Updated on STN: 9 Jan 1991
AB Aspartic acid 244 that occurs at the putative NAD+-binding site of rat liver S-adenosylhomocysteinase was replaced by glutamic acid by oligonucleotide-directed mutagenesis. The mutant enzyme was purified to homogeneity as judged by sodiumm dodecyl sulfate-polyacrylamide gel electrophoresis. Gel permeation chromatography showed that the purified mutant enzyme was a tetramer as is the wild-type enzyme. In contrast to the wild-type enzyme, which possess 1 mol of tightly bound NAD+ per mol of enzyme subunit, the mutant enzyme had only 0.05 mol of NAD+ but contained about 0.5 mol each of NADH and adenine per mol of subunit. The ***mutant*** enzyme, after removal of the bound compounds by acid-ammonium sulfate treatment, exhibited S-***adenosylhomocysteinase*** activity when ***assayed*** in the presence of NAD+. From the appearance of activity as a function of NAD+ concentration, the enzyme was shown to bind NAD+ with a Kd of 23.0 .mu.M at 25.degree. C, a value >280-fold greater than that of the wild-type enzyme. In the presence of a saturating concentration of NAD+, the mutant enzyme showed apparent Km values for substrates similar to those of the wild-type enzyme. Moderate decreases of 8- and 15-fold were observed in Vmax values for the synthetic and hydrolytic directions, respectively. These results indicate the importance of Asp-244 in binding NAD+, and are consistent with the idea that the region of S-adenosylhomocysteinase from residues 213 to 244 is part of the NAD+ binding site. this region has structural features characteristic of the dinucleotide-binding domains of NAD+- and FAD-binding proteins (Ogawa, H., Gomi. T., Mueckler, M. M., Fujioka, M., Backlund, P. S., Jr., Aksamit, R. R., Unson, C. G., and Cantoni, G. L (1987) Proc. Natl. Acad Sci. U. S. A. 84, 719-723).

L4 ANSWER 7 OF 50 TOXCENTER COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:158940 TOXCENTER
COPYRIGHT: Copyright 2005 ACS
DOCUMENT NUMBER: CA11323207411G
TITLE: Site-directed mutagenesis of rat liver S-adenosylhomocysteinase. Effect of conversion of aspartic acid 244 to glutamic acid on coenzyme binding
AUTHOR(S): Gomi, Tomoharu; Takata, Yoshimi; Date, Takayasu; Fujioka, Motoji; Aksamit, Robert R.; Backlund, Peter S., Jr.; Cantoni, Giulio L.
CORPORATE SOURCE: Fac. Med., Toyama Med. Pharm. Univ., Sugitani, 930-01,

Japan.
SOURCE: Journal of Biological Chemistry, (1990) Vol. 265, No. 27, pp. 16102-7.
CODEN: JBCHA3. ISSN: 0021-9258.
COUNTRY: JAPAN
DOCUMENT TYPE: Journal
FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 1990:607411
LANGUAGE: English
ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20021022
AB Aspartic acid (Asp) 244 that occurs at the putative NAD+-binding site of rat liver S-adenosylhomocysteinase was replaced by glutamic acid by oligonucleotide-directed mutagenesis. The mutant enzyme was purified to homogeneity as judged by SDS-PAGE. Gel permeation chromatog. showed that the purified mutant enzyme was a tetramer as is the wild-type enzyme. In contrast to the wild-type enzyme, which possesses 1 mol of tightly bound NAD+ per mol of enzyme subunit, the mutant enzyme had only 0.05 mol of NAD+ but contained .apprx.0.6 mol each of NADH and adenine per mol of subunit. The ***mutant*** enzyme, after removal of the bound compds. by acid(NH)2SO4 treatment, exhibited S- ***adenosylhomocysteinase*** activity when ***assayed*** in the presence of NAD+. From the appearance of activity as a function of NAD+ concn., the enzyme was shown to bind NAD+ with a Kd of 23.0 .mu.M at 25.degree., a value >280-fold greater than that of the wild-type enzyme. In the presence of a satg. concn. of NAD+, the mutant enzyme showed apparent Km values for substrates similar to those of the wild-type enzyme. Moderate decreases of 8- and 15-fold were obsd. in Vmax values for the synthetic and hydrolytic directions, resp. These results indicate the importance of Asp-244 in binding NAD+, and are consistent with the idea that the region of S-adenosylhomocysteinase from residues 213 to 244 is part of the NAD+-binding site. This region has structural features characteristic of the dinucleotide-binding domains of NAD+- and FAD-binding proteins (Ogawa, H. et al., 1987).

L4 ANSWER 8 OF 50 TOXCENTER COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:54288 TOXCENTER
DOCUMENT NUMBER: PubMed ID: 1975808
TITLE: Site-directed mutagenesis of rat liver S-adenosylhomocysteinase. Effect of conversion of aspartic acid 244 to glutamic acid on coenzyme binding
AUTHOR(S): Gomi T; Takata Y; Date T; Fujioka M; Aksamit R R; Backlund P S Jr; Cantoni G L
CORPORATE SOURCE: Department of Biochemistry, Toyama Medical and Pharmaceutical University Faculty of Medicine, Japan
SOURCE: Journal of biological chemistry, (1990 Sep 25) 265 (27) 16102-7.
Journal Code: 2985121R. ISSN: 0021-9258.
COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
FILE SEGMENT: MEDLINE
OTHER SOURCE: MEDLINE 90375464
LANGUAGE: English
ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20011116
AB Aspartic acid 244 that occurs at the putative NAD(+)-binding site of rat liver S-adenosylhomocysteinase was replaced by glutamic acid by oligonucleotide-directed mutagenesis. The mutant enzyme was purified to homogeneity as judged by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Gel permeation chromatography showed that the purified mutant enzyme was a tetramer as is the wild-type enzyme. In contrast to the wild-type enzyme, which possesses 1 mol of tightly bound NAD+ per mol of enzyme subunit, the mutant enzyme had only 0.05 mol of NAD+ but contained about 0.6 mol each of NADH and adenine per mol of subunit. The ***mutant*** enzyme, after removal of the bound compounds by acid-ammonium sulfate treatment, exhibited S- ***adenosylhomocysteinase*** activity when ***assayed*** in the presence of NAD+. From the appearance of activity as a function of NAD+ concentration, the enzyme was shown to bind NAD+ with a Kd of 23.0 microM at 25 degrees C, a value greater than 280-fold greater than that of the

wild-type enzyme. In the presence of a saturating concentration of NAD+, the mutant enzyme showed apparent Km values for substrates similar to those of the wild-type enzyme. Moderate decreases of 8- and 15-fold were observed in Vmax values for the synthetic and hydrolytic directions, respectively. These results indicate the importance of Asp-244 in binding NAD+, and are consistent with the idea that the region of S-adenosylhomocysteinase from residues 213 to 244 is part of the NAD+ binding site. This region has structural features characteristic of the dinucleotide-binding domains of NAD(+)- and FAD-binding proteins (Ogawa, H., Gomi, T., Mueckler, M. M., Fujioka, M., Backlund, P.S., Jr., Aksamit, R.R., Unson, C.G., and Cantoni, G.L. (1987) Proc. Natl. Acad. Sci. U.S.A. 84, 719-723).

L4 ANSWER 9 OF 50 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 2003:37449532 BIOTECHNO
TITLE: Gene expression profile in diabetic KK/Ta mice
AUTHOR: Fan Q.; Shike T.; Shigihara T.; Tanimoto M.; Gohda T.; Makita Y.; Wang L.N.; Horikoshi S.; Tomino Y.
CORPORATE SOURCE: Y. Tomino, Division of Nephrology, Department of Internal Medicine, Juntendo Univ. School of Medicine, 2-1-1 Hongo, Bunkyoku, Tokyo 113-8421, Japan. E-mail: yasu@med.juntendo.ac.jp
SOURCE: Kidney International, (2003), 64/6 (1978-1985), 30 reference(s)
CODEN: KDYIA5 ISSN: 0085-2538
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2003:37449532 BIOTECHNO
AB Background. To identify susceptibility genes for diabetic nephropathy, GeneChip.RTM. Expression Analysis was employed to survey the gene expression profile of diabetic KK/Ta mouse kidneys. ***Methods*** . Kidneys from three KK/Ta and two BALB/c mice at 20 weeks of age were dissected. Total RNA was extracted and labeled for hybridizing to the Affymetrix Murine Genome U74Av2 array. The gene expression profile was compared between KK/Ta and BALB/c mice using GeneChip.RTM. expression analysis software. Competitive reverse transcription-polymerase chain reaction (RT-PCR) was used to confirm the results of GeneChip.RTM. for a selected number of genes. Results. Out of 12,490 probe pairs present on GeneChip.RTM., 98 known genes and 31 expressed sequence tags (ESTs) were found to be differentially expressed between KK/Ta and BALB/c kidneys. Twenty-one known genes and seven ESTs that increased in expression and 77 known genes and 24 ESTs that decreased in KK/Ta kidneys were identified. These genes are related to renal function, extracellular matrix expansion and degradation, signal transduction, transcription regulation, ion transport, glucose and lipid metabolism, and protein synthesis and degradation. In the vicinity of UA-1 (quantitative trait locus for the development of albuminuria in KK/Ta mice), candidate genes that showed differential expression were identified, including the Sdc4 gene for syndecan-4, Ahcy gene for S- ***adenosylhomocysteine*** ***hydrolase*** , Sstr4 gene for somatostatin receptor 4, and MafB gene for Kreisler leucine zipper protein. Conclusion. The gene expression profile in KK/Ta kidneys is different from that in age-matched BALB/c kidneys. ***Altered*** gene expressions in the vicinity of UA-1 may be responsible for the development of albuminuria in diabetic KK/Ta mice.

L4 ANSWER 10 OF 50 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN ✓
ACCESSION NUMBER: 2003:37034159 BIOTECHNO
TITLE: Structure, evolution, and inhibitor interaction of S-adenosyl-L-homocysteine hydrolase from Plasmodium falciparum
AUTHOR: Bujnicki J.M.; Prigge S.T.; Caridha D.; Chiang P.K.
CORPORATE SOURCE: J.M. Bujnicki, Bioinformatics Laboratory, Intl. Inst. of Molec./Cell Biology, 02-109 Warsaw, Poland. E-mail: iamb@genesilico.pl
SOURCE: Proteins: Structure, Function and Genetics, (01 SEP 2003), 52/4 (624-632), 27 reference(s)
CODEN: PSFGEY ISSN: 0887-3585
DOCUMENT TYPE: Journal; Article

COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2003:37034159 BIOTECHNO
AB S- ***adenosylhomocysteine*** ***hydrolase*** (SAHH) is a key regulator of S-adenosylmethionine-dependent methylation reactions and an interesting pharmacologic target. We cloned the SAHH gene from Plasmodium falciparum (PfSAHH), with an amino acid sequence agreeing with that of the PlasmoDB genomic database. Even though the expressed recombinant enzyme, PfSAHH, could use 3-deaza-adenosine (DZA) as an ***alternative*** substrate in contrast to the human SAHH, it has a unique inability to substitute 3-deaza-(.+-.)aristeromycin (DZAri) for adenosine. Among the analogs of DZA, including neplanocin A, DZAri was the most potent inhibitor of the PfSAHH enzyme activity, with a K.sub.i of about 150 nM, whether Ado or DZA was used as a substrate. When the same DZA analogs were ***tested*** for their antimalarial activity, they also inhibited the in vitro growth of P. falciparum parasites potently. Homology-modeling analysis revealed that a single substitution (Thr60-Cys59) between the human and malarial PfSAHH, in an otherwise similar SAH-binding pocket, might account for the differential interactions with the nucleoside analogs. This subtle difference in the active site may be exploited in the development of novel drugs that selectively inhibit PfSAHH. We performed a comprehensive phylogenetic analysis of the SAHH superfamily and inferred that SAHH evolved in the common ancestor of Archaea and Eukaryota, and was subsequently horizontally transferred to Bacteria. Additionally, an analysis of the unusual and uncharacterized AHCYL1 family of the SAHH paralogs extant only in animals reveals striking divergence of its SAH-binding pocket and the loss of key conserved residues, thus suggesting an evolution of novel function(s). .COPYRGT. 2003 Wiley-Liss, Inc.

L4 ANSWER 11 OF 50 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 2002:34967245 BIOTECHNO
TITLE: Catalytic mechanism of S-adenosylhomocysteine hydrolase. Site-directed mutagenesis of Asp-130, Lys-185, Asp-189, and Asn31-190
AUTHOR: Takata Y.; Yamada T.; Huang Y.; Komoto J.; Gomi T.; Ogawa H.; Fujioka M.; Takusagawa F.
CORPORATE SOURCE: F. Takusagawa, Dept. of Molecular Biosciences, 3004 Haworth Hall, University of Kansas, 1200 Sunnyside Ave., Lawrence, KS 66045-7534, United States.
E-mail: xraymain@ku.edu
SOURCE: Journal of Biological Chemistry, (21 JUN 2002), 277/25 (22670-22676), 16 reference(s)
CODEN: JBCHA3 ISSN: 0021-9258
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2002:34967245 BIOTECHNO
AB S- ***Adenosylhomocysteine*** ***hydrolase*** (***AdoHcyase***) catalyzes the hydrolysis of S- ***adenosylhomocysteine*** to form adenosine and homocysteine. On the bases of crystal structures of the wild type enzyme and the D244E ***mutated*** enzyme complexed with 3'-keto-adenosine (D244E.midldot.Ado*), we have identified the important amino acid residues, Asp-130, Lys-185, Asp-189, and Asn-190, for the catalytic reaction and have proposed a catalytic mechanism (Komoto, J., Huang, Y., Gomi, T., Ogawa, H., Takata, Y., Fujioka, M., and Takusagawa, F. (2000) J. Biol. Chem. 275, 32147-32156). To confirm the proposed catalytic mechanism, we have made the D130N, K185N, D189N, and N190S ***mutated*** enzymes and ***measured*** the catalytic activities. The catalytic rates (k.sub.c.sub.a.sub.t) of D130N, K185N, D189N, and N190S ***mutated*** enzymes are reduced to 0.7%, 0.5%, 0.1%, and 0.5%, respectively, in comparison with the wild type enzyme, indicating that Asp-130, Lys-185, Asp-189, and Asn-190 are involved in the catalytic reaction. K.sub.m values of the ***mutated*** enzymes are increased significantly, except for the N190S ***mutation*** , suggesting that Asp-130, Lys-185, and Asp-189 participate in the substrate binding. To interpret the kinetic data, the oxidation states of the bound NAD molecules of the wild type and ***mutated*** enzymes were

measured during the catalytic reaction by monitoring the absorbance at 340 nm. The crystal structures of the WT and D244E.midldot.Ado*, containing four subunits in the crystallographic asymmetric unit, were re-refined to have the same subunit structures. A detailed catalytic mechanism of ***AdoHcyase*** has been revealed based on the oxidation states of the bound NAD and the re-refined crystal structures of WT and D244E.midldot.Ado*. Lys-185 and Asp-130 abstract hydrogen atoms from 3'-OH and 4'-CH, respectively. Asp-189 removes a proton from Lys-185 and produces the neutral N.zeta. (-NH.sub.2), and Asn-190 facilitates formation of the neutral Lys-185. His-54 and His-300 hold and polarize a water molecule, which nucleophilically attacks the C5'- of 3'-keto-4',5'-dehydroadenosine to produce 3'-keto-Ado.

L4 ANSWER 12 OF 50 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 2002:34966731 BIOTECHNO
TITLE: Altered levels of S-adenosylmethionine and S-adenosylhomocysteine in the brains of L-isoaspartyl (D-aspartyl) O-methyltransferase-deficient mice
AUTHOR: Farrar C.; Clarke S.
CORPORATE SOURCE: S. Clarke, 640 Paul D. Boyer Hall, 611 Charles E. Young Drive East, Los Angeles, CA 90095-1570, United States.
E-mail: clarke@mbi.ucla.edu
SOURCE: Journal of Biological Chemistry, (02 AUG 2002), 277/31 (27856-27863), 55 reference(s)
CODEN: JBCHA3 ISSN: 0021-9258
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2002:34966731 BIOTECHNO
AB L-Isoaspartyl (D-aspartyl) O-methyltransferase (PCMT1) is a protein repair enzyme that initiates the conversion of abnormal D-aspartyl and L-isoaspartyl residues to the normal L-aspartyl form. In the course of this reaction, PCMT1 converts the methyl donor S-adenosyl-methionine (AdoMet) to S- ***adenosylhomocysteine*** (AdoHcy). Due to the high level of activity of this enzyme, particularly in the brain, it seemed of interest to investigate whether the lack of PCMT1 activity might ***alter*** the concentrations of these small molecules. AdoMet and AdoHcy were ***measured*** in mice lacking PCMT1 (Pcmt1-/-), as well as in their heterozygous (Pcmt1+/-) and wild type (Pcmt1+/+) littermates. Higher levels of AdoMet and lower levels of AdoHcy were found in the brains of Pcmt1-/- mice, and to a lesser extent in Pcmt1+/- mice, when compared with Pcmt1+/+ mice. In addition, these levels appear to be most significantly ***altered*** in the hippocampus of the Pcmt1-/- mice. The changes in the AdoMet/AdoHcy ratio could not be attributed to increases in the activities of methionine adenosyltransferase II or S-***adenosylhomocysteine*** ***hydrolase*** in the brain tissue of these mice. Because changes in the AdoMet/AdoHcy ratio could potentially ***alter*** the overall excitatory state of the brain, this effect may play a role in the progressive epilepsy seen in the Pcmt1-/- mice.

L4 ANSWER 13 OF 50 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 2002:34851643 BIOTECHNO
TITLE: In the cystathionine .beta.-synthase knockout mouse, elevations in total plasma homocysteine increase tissue S-adenosylhomocysteine, but responses of S-adenosylmethionine and DNA methylation are tissue specific
AUTHOR: Choumenkovitch S.F.; Selhub J.; Bagley P.J.; Maeda N.; Nadeau M.R.; Smith D.E.; Choi S.-W.
CORPORATE SOURCE: S.-W. Choi, Vitamin Metabolism Laboratory, Jean Mayer U.S. Dept. of Agriculture, Human Nutr. Research Center on Aging, Boston, MA 02111, United States.
E-mail: schoi@hnrc.tufts.edu
SOURCE: Journal of Nutrition, (2002), 132/8 (2157-2160), 26 reference(s)
CODEN: JONUAI ISSN: 0022-3166
DOCUMENT TYPE: Journal; Article
COUNTRY: United States

LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2002:34851643 BIOTECHNO
AB The cystathionine .beta.- ***synthase*** knockout mouse provides a unique opportunity to study biochemical consequences of a defective cystathionine .beta.- ***synthase*** enzyme. The present study was undertaken to assess the effect of elevated plasma total homocysteine caused by cystathionine .beta.- ***synthase*** deficiency on one-carbon metabolism in 10 homozygous ***mutant*** mice and 10 age- and sex-matched wild-type mice. Plasma total homocysteine levels, S-adenosylmethionine and S- ***adenosylhomocysteine*** concentrations in liver, kidney and brain were ***measured*** by HPLC. Tissue DNA methylation status was ***measured*** by in vitro DNA methyl acceptance. Plasma total homocysteine concentration in food-deprived homozygous ***mutant*** mice (271.1 .+-. 61.5 .mu.mol/L) was markedly higher than in wild-type mice (7.4 .+-. 2.9 .mu.mol/L) ($P < 0.001$). In liver only, S-adenosylmethionine concentrations were higher in the homozygous ***mutant*** mice (35.6 .+-. 5.9 nmol/g) than in wild type mice (19.1 .+-. 6.1 nmol/g) ($P < 0.001$) and tended to be lower in kidney ($P = 0.07$). In contrast, S- ***adenosylhomocysteine*** concentrations were significantly higher in homozygous ***mutant*** mice compared with wild-type mice in all tissues studied. Genomic DNA methylation status in homozygous ***mutant*** compared with wild-type mice was lower in liver ($P = 0.037$) and tended to be lower in kidney ($P = 0.077$) but did not differ in brain ($P = 0.46$). The results of this study are consistent with the predicted role of cystathionine .beta.- ***synthase*** in the regulation of plasma total homocysteine levels and tissue S- ***adenosylhomocysteine*** levels. However, the fact that the absence of the enzyme had differential effects on S-adenosylmethionine concentrations and DNA methylation status in different tissues suggests that regulation of biological methylation is a complex tissue-specific phenomenon.

L4 ANSWER 14 OF 50 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 2001:32614021 BIOTECHNO
TITLE: Homocysteine metabolism in children with down syndrome: In vitro modulation
AUTHOR: Pogribna M.; Melnyk S.; Pogribny I.; Chango A.; Yi P.; James S.J.
CORPORATE SOURCE: Dr. S.J. James, Natl. Ctr. for Toxicological Res., 3900 NCTR Road, Jefferson, AR 72079, United States. E-mail: jjames@nctr.fda.gov
SOURCE: American Journal of Human Genetics, (2001), 69/1 (88-95), 38 reference(s)
CODEN: AJHGAG ISSN: 0002-9297
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2001:32614021 BIOTECHNO
AB The gene for cystathionine .beta.- ***synthase*** (CBS) is located on chromosome 21 and is overexpressed in children with Down syndrome (DS), or trisomy 21. The dual purpose of the present study was to evaluate the impact of overexpression of the CBS gene on homocysteine metabolism in children with DS and to determine whether the supplementation of trisomy 21 lymphoblasts in vitro with selected nutrients would shift the genetically induced metabolic imbalance. Plasma samples were obtained from 42 children with karyotypically confirmed full trisomy 21 and from 36 normal siblings (mean age 7.4 years). Metabolites involved in homocysteine metabolism were ***measured*** and compared to those of normal siblings used as controls. Lymphocyte DNA methylation status was determined as a functional endpoint. The results indicated that plasma levels of homocysteine, methionine, S- ***adenosylhomocysteine*** , and S-adenosylmethionine were all significantly decreased in children with DS and that their lymphocyte DNA was hypermethylated relative to that in normal siblings. Plasma levels of cystathionine and cysteine were significantly increased, consistent with an increase in CBS activity. Plasma glutathione levels were significantly reduced in the children with DS and may reflect an increase in oxidative stress due to the overexpression of the superoxide dismutase gene, also located on

chromosome 21. The addition of methionine, folinic acid, methyl-B.sub.1.sub.2, thymidine, or dimethylglycine to the cultured trisomy 21 lymphoblastoid cells improved the metabolic profile in vitro. The increased activity of CBS in children with DS significantly ***alters*** homocysteine metabolism such that the folate-dependent resynthesis of methionine is compromised. The decreased availability of homocysteine promotes the well-established "folate trap," creating a functional folate deficiency that may contribute to the metabolic pathology of this complex genetic disorder.

L4 ANSWER 15 OF 50 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1996:26374604 BIOTECHNO
TITLE: Chemical modification and site-directed mutagenesis of cysteine residues in human placental S-adenosylhomocysteine hydrolase
AUTHOR: Yuan C.-S.; Ault-Riche D.B.; Borchardt R.T.
CORPORATE SOURCE: Simons Research Laboratories, Dept. of Pharmaceutical Chemistry, University of Kansas, 2095 Constant Ave.,Lawrence, KS 66047, United States.
SOURCE: Journal of Biological Chemistry, (1996), 271/45 (28009-28016)
CODEN: JBCHA3 ISSN: 0021-9258
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1996:26374604 BIOTECHNO
AB Human placental S- ***adenosylhomocysteine*** (AdoHcy) ***hydrolase*** (EC 3.3.1.1) was inactivated by 5',5-dithiobis(2-nitrobenzoic acid) following pseudo- first-order kinetics. Modification of three of the 10 cysteine residues per enzyme subunit resulted in complete inactivation of the enzyme. The three modified cysteine residues were identified as Cys.sup.1.sup.1.sup.3, Cys.sup.1.sup.9.sup.5, and Cys.sup.4.sup.2.sup.1, respectively, by protein sequencing after modification with .cents.1- .sup.1.sup.4C!i-odoacetamide. Of the three modifiable cysteines, Cys.sup.1.sup.1.sup.9 and Cys.sup.1.sup.9.sup.5 could be protected from modification in the presence of the substrate adenosine (Ado), which also protected the enzyme from inactivation. On the other hand, Cys.sup.4.sup.2.sup.1 was not protected by Ado, and modification of Cys.sup.4.sup.2.sup.1 alone did not affect the enzyme activity. To verify whether some of these cysteine residues are important for the enzyme catalysis, these three cysteine residues were replaced by either serine or aspartic acid using site- directed mutagenesis. ***Mutants*** of both Cys.sup.1.sup.1.sup.3 (C113S and C113D) and Cys.sup.4.sup.2.sup.1 (C421S and C421D) had enzyme activities similar to that of the wild-type enzyme, and only slight changes were observed in the steady-state kinetics ***measured*** in both the synthetic and hydrolytic directions. However, ***mutants*** of Cys.sup.1.sup.9.sup.5 (C195D and C195S) displayed drastically reduced enzyme activities, and k(cat) values were only 7 and 12% of that of the wild-type enzyme, respectively, resulting in a calculated loss in binding energy (AAG) of approximate 1 Kcal/mol. The Cys.sup.1.sup.9.sup.5 ***mutants*** were capable of catalyzing both the 3'-oxidative and 5'-hydrolytic reactions, as evidenced by the reduction of E-NAD.sup.+ to NADH and formation of the 5'-hydrolytic product when incubated with (E)-5',6'-didehydro-6'-deoxy-6'-chlorohomoadeno-sine at rates comparable with those catalyzed by the wild-type enzyme. However, ***mutations*** of the Cys.sup.1.sup.9.sup.5 severely ***altered*** the 3'-reduction potential as evidenced by the drastic reduction in the rate of .cents.2,8-.sup.3H!Ado release from the E-NADH- .cents.2,8-.sup.3H!3'-keto-Ado complex. Circular dichroism studies of the Cys.sup.1.sup.9.sup.5 ***mutants*** confirmed that the observed effects are not due to changes in secondary structure. These results suggested that the Cys.sup.1.sup.9.sup.5 is involved in the catalytic center and may play an important role in maintaining the 3'- reduction potential for effective release of the reaction products and regeneration of the active form (NAD.sup.+ form) of the enzyme; the Cys.sup.1.sup.1.sup.3 is located in or near the substrate binding site, but plays no role beneficial to the catalysis; and the Cys.sup.4.sup.2.sup.1 is a nonessential residue, which also explains why Cys.sup.4.sup.2.sup.1 does not occur in any other known

AdoHcy ***hydrolases*** .

L4 ANSWER 16 OF 50 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1994:24124513 BIOTECHNO
TITLE: The mouse lethal nonagouti (a(x)) mutation deletes the S-adenosylhomocysteine hydrolase (Ahcy) gene
AUTHOR: Miller M.W.; Duhl D.M.J.; Winkes B.M.; Arredondo-Vega F.; Saxon P.J.; Wolff G.L.; Epstein C.J.; Hershfield M.S.; Barsh G.S.
CORPORATE SOURCE: Department of Pediatrics, Howard Hughes Medical Institute, Stanford University School Medicine,Stanford, CA 94305-5428, United States.
SOURCE: EMBO Journal, (1994), 13/8 (1806-1816)
CODEN: EMJODG ISSN: 0261-4189
DOCUMENT TYPE: Journal; Article
COUNTRY: United Kingdom
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1994:24124513 BIOTECHNO
AB The lethal nonagouti (a(x)) ***mutation*** is a hypomorphic allele of the agouti coat color locus which, when homozygous, also leads to embryonic death around the time of implantation. To understand the molecular basis of these phenotypes, we identified and cloned a deletion breakpoint junction present in the a(x) chromosome. Long range restriction mapping demonstrated a simple deletion of .sim. 100 kb, which does not affect agouti coding sequences, but begins only 4 kb 3' of the last exon, and thus may affect coat color by removing an agouti 3' enhancer. The Ahcy gene, which codes for the enzyme S-***adenosylhomocysteine*** ***hydrolase*** (***SAHase***), is contained within a 20 kb region within the a(x) deletion. ***SAHase*** RNA and protein were ***detectable*** in early blastocysts and in embryonic stem cells, respectively, and analysis of embryos derived from an a(x)/a x a(x)/a embryo intercross indicated that a(x)/a embryos die between the late blastocyst and early implantation stages. Treatment of cultured embryos with an ***SAHase*** inhibitor, 3-deazaaristeromycin, or with metabolites that can result in elevated levels of cellular SAH, resulted in an inhibition of inner cell mass development, suggesting that loss of ***SAHase*** activity in a(x)/a(x) embryos is sufficient to explain their death around the time of implantation.

L4 ANSWER 17 OF 50 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1990:20324474 BIOTECHNO
TITLE: Site-directed mutagenesis of rat liver S-adenosylhomocysteinase. Effect of conversion of aspartic acid 244 to glutamic acid on coenzyme binding
AUTHOR: Gomi T.; Takata Y.; Date T.; Fujioka M.; Aksamit R.R.; Backlund Jr. P.S.; Cantoni G.L.
CORPORATE SOURCE: Dept. of Biochemistry, Faculty of Medicine, Toyama Med./Pharma. Univ., 2630 Sugitani,Toyama 930-01, Japan.
SOURCE: Journal of Biological Chemistry, (1990), 265/27 (16102-16107)
CODEN: JBCHA3 ISSN: 0021-9258
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1990:20324474 BIOTECHNO
AB Aspartic acid 244 that occurs at the putative NAD.sup.+-binding site of rat liver S- ***adenosylhomocysteinase*** was replaced by glutamic acid by oligonucleotide-directed mutagenesis. The ***mutant*** enzyme was purified to homogeneity as judged by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Gel permeation chromatography showed that the purified ***mutant*** enzyme was a tetramer as is the wild-type enzyme. In contrast to the wild-type enzyme, which possesses 1 mol of tightly bound NAD.sup.+ per mol of enzyme subunit, the ***mutant*** enzyme had only 0.05 mol of NAD.sup.+ but contained about 0.6 mol each of NADH and adenine per mol of subunit. The ***mutant*** enzyme, after removal of the bound compounds by acid-ammonium sulfate

treatment, exhibited S- ***adenosylhomocysteinase*** activity when ***assayed*** in the presence of NAD.sup.+. From the appearance of activity as a function of NAD.sup.+ concentration, the enzyme was shown to bind NAD.sup.+ with a K(d) of 23.0 .mu.M at 25 .degree.C, a value >280-fold greater than that of the wild-type enzyme. In the presence of a saturating concentration of NAD.sup.+, the ***mutant*** enzyme showed apparent K(m) values for substrates similar to those of the wild-type enzyme. Moderate decreases of 8- and 15-fold were observed in V(max) values for the synthetic and hydrolytic directions, respectively. These results indicate the importance of Asp-244 in binding NAD.sup.+, and are consistent with the idea that the region of S- ***adenosylhomocysteinase*** from residues 213 to 244 is part of the NAD.sup.+ binding site. This region has structural features characteristic of the dinucleotide-binding domains of NAD.sup.+- and FAD-binding proteins (Ogawa, H., Gomi, T., Mueckler, M. M., Fujioka, M., Backlund, P. S., Jr., Aksamit, R. R., Unson, C. G., and Cantoni, G. L. (1987) (1978) Proc. Natl. Acad. Sci. U.S.A. 84, 719-723).

L4 ANSWER 18 OF 50 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1988:18272529 BIOTECHNO
TITLE: The map of chromosome 20
AUTHOR: Simpson N.E.
CORPORATE SOURCE: Division of Medical Genetics, Department of Paediatrics, Queen's University, Kingston, Ont. K7L 3N6, Canada.
SOURCE: Journal of Medical Genetics, (1988), 25/12 (794-804)
CODEN: JMDGAE ISSN: 0022-2593
DOCUMENT TYPE: Journal; Article
COUNTRY: United Kingdom
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1988:18272529 BIOTECHNO
AB The number of gene assignments of human chromosome 20 has inreased slowly until recently. Only seven genes and one fragile site were confirmed assignments to chromosome 20 at the Ninth Human Gene Mapping Workshop in September 1987 (HGM9). One fragile site, 13 additional genes, and 10 DNA sequences that identify restriction fragment length polymorphisms (RFLPs), however, were provisionally added to the map at HGM9. Five ***mutated*** genes on chromosome 20 have a relation to disease: a ***mutation*** in the adenosine deaminase gene results in a deficiency of the enzyme and severe combined immune deficiency; ***mutations*** in the gene for the growth hormone releasing factor result in some forms of dwarfism; ***mutations*** in the closely linked genes for the hormones arginine vasopressin and oxytocin and their neurophysins are probably responsible for some diabetes insipidus; and ***mutations*** in the gene that regulates both .alpha.-neuraminidase and .beta.-galactosidase activities determine galactosialidosis. The gene for the prion protein is on chromosome 20; it is related to the infectious agent of kuru, Creutzfeld-Jacob disease, and Gertsmann-Straussler syndrome, although the nature of the relationship is not completely understood. Two genes that code for tyrosine kinases are on the chromosome, SRC1 the proto-oncogene and a gene (HCK) coding for haemopoietic kinase (an src-like kinase), but no direct relation to cancer has been shown for either of these kinases. The significance of non-random loss of chromosome 20 in the malignant diseases non-lymphocytic leukaemia and polycythaemia vera is not understood. Twenty-four additional loci are assigned to the chromosome: five genes that code for binding proteins, one for a light chain of ferritin, genes for three enzymes (inosine triphosphatase, s- ***adenosylhomocysteine*** ***hydrolase*** , and sterol delta 24-reductase), one for each of a secretory protein and an opiate neuropeptide, a cell surface antigen, two fragile sites, and 10 DNA sequences (one satellite and nine unique) that ***detect*** RFLPs.

L4 ANSWER 19 OF 50 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1987:17086236 BIOTECHNO
TITLE: Neplanocin A inhibition of S-adenosylhomocysteine hydrolase in Alcaligenes faecalis has no effect on growth of the microorganism
AUTHOR: Fisher E.W.; Decedue C.J.; Keller B.T.; Borchardt R.T.

CORPORATE SOURCE: Department of Biochemistry, University of Kansas, Lawrence, KS 66045, United States.
SOURCE: Journal of Antibiotics, (1987), 40/6 (873-881)
CODEN: JANTAJ
DOCUMENT TYPE: Journal; Article
COUNTRY: Japan
LANGUAGE: English
AN 1987:17086236 BIOTECHNO
AB Neplanocin A, a cyclopentyl analog of adenosine, is a naturally occurring antibiotic possessing potent inhibitory activity toward the enzyme S-***adenosylhomocysteine*** (AdoHcy) ***hydrolase*** . In the present study, we examined whether there was a correlation between the inhibition of prokaryotic AdoHcy ***hydrolase*** and the reported antibacterial activity of neplanocin A, e.g. Alcaligenes faecalis (Yaginuma et al., J. Antibiotics 34: 359-366, 1981). Of 16 bacterial species screened, only 2 organisms (both of which contained AdoHcy ***hydrolase***) were sensitive to 10 nM neplanocin A when grown on agar plates. None of the 16 strains showed any growth sensitivity in broth culture to concentrations of the antibiotic as high as 4 mM. However, treatment of A. faecalis broth culture with 14 .mu.M neplanocin A resulted in complete inhibition of cellular AdoHcy ***hydrolase*** and subsequent elevation of intracellular AdoHcy. No ***alternative*** ***method*** for degrading or removing the excess AdoHcy from these cells was ***detected*** . Bacillus subtilis, which exhibited no AdoHcy ***hydrolase*** activity showed no ***alteration*** of AdoHcy metabolism when treated with the same concentration of the antibiotic. These results indicate that inhibition of AdoHcy ***hydrolase*** is not related to the antibacterial activity of neplanocin A and suggest that using this enzyme as a target for the design of antimicrobial agents is not likely to prove a productive approach.

L4 ANSWER 20 OF 50 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1983:13100518 BIOTECHNO
TITLE: Characterization of adenosine deaminase-deficient human histiocytic lymphoma cell line (DHL-9) and selection of mutants deficient in adenosine kinase and deoxycytidine kinase
AUTHOR: Kubota M.; Kamatani N.; Daddona P.E.; Carson D.A.
CORPORATE SOURCE: Dep. Basic Clin. Res., Scripps Clin. Res. Found., La Jolla, CA 92037, United States.
SOURCE: Cancer Research, (1983), 43/6 (2606-2610)
CODEN: CNREA8
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
AN 1983:13100518 BIOTECHNO
AB The association of adenosine deaminase (ADA) deficiency with immunodeficiency disease has emphasized the importance of this purine metabolic enzyme for human lymphocyte growth and function. This report describes the natural occurrence of ADA deficiency in a human histiocytic lymphoma cell line, DHL-9. The minimal ADA activity in DHL-9 extracts, 0.028 nmol/min/mg protein, was less than 50% of the activity in two B-lymphoblastoid cell lines from ADA-deficient patients and was resistant to the potent ADA inhibitor deoxycoformycin. A sensitive radioimmunoassay failed to ***detect*** immunoreactive ADA in DHL-9 cells. Moreover, in DHL-9 cells, deoxycoformycin did not augment either the growth-inhibitory effects of adenosine and deoxyadenosine or the accumulation of deoxyadenosine triphosphate from deoxyadenosine. When compared to six other human hematopoietic cell lines. DHL-9 had 5,6-fold-higher levels of adenosyl-homocysteinase. Chromosome 20, which bears the structural gene for ADA and ***adenosylhomocysteinase*** , was diploid and had a normal Giemsa banding pattern. The parental DHL-9 cell line was used for the selection and cloning of secondary ***mutants*** deficient in deoxycytidine kinase and adenosine kinase.

L4 ANSWER 21 OF 50 LIFESCI COPYRIGHT 2005 CSA on STN
ACCESSION NUMBER: 2004:77694 LIFESCI
TITLE: Uteroplacental insufficiency alters DNA methylation, one-carbon metabolism, and histone acetylation in IUGR rats
AUTHOR: MacLennan, N.K.; James, S.J.; Melnyk, S.; Piroozi, A.;

Jernigan, S.; Hsu, J.L.; Janke, S.M.; Pham, T.D.; Lane, R.H.
CORPORATE SOURCE: David Geffen School of Medicine, UCLA, Department of Pediatrics, Division of Neonatology and Developmental Biology, Mattel Children's Hospital, UCLA, Los Angeles, California, 90095-1752, USA
SOURCE: Physiological Genomics [Physiol. Genomics], (20040600) vol. 18, no. 1, pp. 43-50.
ISSN: 1094-8341.
DOCUMENT TYPE: Journal
FILE SEGMENT: G; N
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Uteroplacental insufficiency leads to intrauterine growth retardation (IUGR) and increases the risk of insulin resistance and hypertriglyceridemia in both humans and rats. Postnatal changes in hepatic gene expression characterize the postnatal IUGR rat, despite the transient nature of the initial in utero insult. Phenomena such as DNA methylation and histone acetylation can induce a relatively static reprogramming of gene transcription by ***altering*** chromatin infrastructure. We therefore hypothesized that uteroplacental insufficiency persistently affects DNA methylation and histone acetylation in the IUGR rat liver. IUGR rat pups were created by inducing uteroplacental insufficiency through bilateral uterine artery ligation of the pregnant dam on day 19 of gestation. The SssI methyltransferase ***assay*** and two-dimensional thin-layer chromatography demonstrated genome-wide DNA hypomethylation in postnatal IUGR liver. To investigate a possible mechanism for this hypomethylation, levels of hepatic metabolites and enzyme mRNAs involved in one-carbon metabolism were ***measured*** using HPLC with coulometric electrochemical ***detection*** and real-time RT-PCR, respectively. Uteroplacental insufficiency increased IUGR levels of S-***adenosylhomocysteine*** , homocysteine, and methionine in association with decreased mRNA levels of methionine adenosyltransferase and cystathionine- beta - ***synthase*** . Western blotting further demonstrated that increased quantities of acetylated histone H3 also characterized the IUGR liver. Increased hepatic levels of S-***adenosylhomocysteine*** can promote DNA hypomethylation, which is often associated with histone hyperacetylation. We speculate that the ***altered*** intrauterine milieu associated with uteroplacental insufficiency affects hepatic one-carbon metabolism and subsequent DNA methylation, which thereby ***alters*** chromatin dynamics and leads to persistent changes in hepatic gene expression.

L4 ANSWER 22 OF 50 LIFESCI COPYRIGHT 2005 CSA on STN ✓
ACCESSION NUMBER: 2003:85413 LIFESCI
TITLE: Structure, evolution, and inhibitor interaction of S-adenosyl-L- homocysteine hydrolase from Plasmodium falciparum
AUTHOR: Bujnicki, J.M.; Prigge, S.T.; Caridha, D.; Chiang, P.K.
CORPORATE SOURCE: Bioinformatics Laboratory, International Institute of Molecular and Cell Biology, 02-109 Warsaw, Poland; E-mail: iamb@genesilico.pl
SOURCE: Proteins: Structure, Function & Genetics [Proteins: Struct. Funct. Genet.], (20030000) vol. 52, no. 4, pp. 624-632.
ISSN: 0887-3585.
DOCUMENT TYPE: Journal
FILE SEGMENT: K
LANGUAGE: English
SUMMARY LANGUAGE: English
AB S- ***adenosylhomocysteine*** ***hydrolase*** (SAHH) is a key regulator of S- adenosylmethionine-dependent methylation reactions and an interesting pharmacologic target. We cloned the SAHH gene from Plasmodium falciparum (PfSAHH), with an amino acid sequence agreeing with that of the PlasmoDB genomic database. Even though the expressed recombinant enzyme, PfSAHH, could use 3- deaza-adenosine (DZA) as an ***alternative*** substrate in contrast to the human SAHH, it has a unique inability to substitute 3-deaza-(+/-)aristeromycin (DZAri) for adenosine. Among the analogs of DZA, including neplanocin A, DZAri was the most potent inhibitor of the PfSAHH enzyme activity, with a K sub(i) of about 150 nM, whether Ado or DZA was used as a substrate. When the same DZA analogs were

tested for their antimalarial activity, they also inhibited the in vitro growth of P. falciparum parasites potently. Homology-modeling analysis revealed that a single substitution (Thr60-Cys59) between the human and malarial PfSAHH, in an otherwise similar SAH-binding pocket, might account for the differential interactions with the nucleoside analogs. This subtle difference in the active site may be exploited in the development of novel drugs that selectively inhibit PfSAHH. We performed a comprehensive phylogenetic analysis of the SAHH superfamily and inferred that SAHH evolved in the common ancestor of Archaea and Eukaryota, and was subsequently horizontally transferred to Bacteria. Additionally, an analysis of the unusual and uncharacterized AHCYL1 family of the SAHH paralogs extant only in animals reveals striking divergence of its SAH-binding pocket and the loss of key conserved residues, thus suggesting an evolution of novel function(s).

L4 ANSWER 23 OF 50 LIFESCI COPYRIGHT 2005 CSA on STN
ACCESSION NUMBER: 2002:96291 LIFESCI
TITLE: Altered Levels of S-Adenosylmethionine and S-Adenosylhomocysteine in the Brains of L-Isoaspartyl (D-Aspartyl) O-Methyltransferase-deficient Mice
AUTHOR: Farrar, C.; Clarke, S.
CORPORATE SOURCE: Department of Chemistry, UCLA, Los Angeles, California 90095-1569, USA; E-mail: clarke@mbi.ucla.edu
SOURCE: Journal of Biological Chemistry [J. Biol. Chem.], (20020802) vol. 277, no. 31, pp. 27856-27863.
ISSN: 0021-9258.
DOCUMENT TYPE: Journal
FILE SEGMENT: G; N3
LANGUAGE: English
SUMMARY LANGUAGE: English
AB L-Isoaspartyl (D-aspartyl) O-methyltransferase (PCMT1) is a protein repair enzyme that initiates the conversion of abnormal D-aspartyl and L-isoaspartyl residues to the normal L-aspartyl form. In the course of this reaction, PCMT1 converts the methyl donor S-adenosylmethionine (AdoMet) to S- ***adenosylhomocysteine*** (AdoHcy). Due to the high level of activity of this enzyme, particularly in the brain, it seemed of interest to investigate whether the lack of PCMT1 activity might ***alter*** the concentrations of these small molecules. AdoMet and AdoHcy were ***measured*** in mice lacking PCMT1 (Pcmt1-/-), as well as in their heterozygous (Pcmt1+/-) and wild type (Pcmt1+/+) littermates. Higher levels of AdoMet and lower levels of AdoHcy were found in the brains of Pcmt1-/- mice, and to a lesser extent in Pcmt1+/- mice, when compared with Pcmt1+/+ mice. In addition, these levels appear to be most significantly ***altered*** in the hippocampus of the Pcmt1-/- mice. The changes in the AdoMet/AdoHcy ratio could not be attributed to increases in the activities of methionine adenosyltransferase II or S-***adenosylhomocysteine*** ***hydrolase*** in the brain tissue of these mice. Because changes in the AdoMet/AdoHcy ratio could potentially ***alter*** the overall excitatory state of the brain, this effect may play a role in the progressive epilepsy seen in the Pcmt1-/- mice.

L4 ANSWER 24 OF 50 LIFESCI COPYRIGHT 2005 CSA on STN
ACCESSION NUMBER: 2002:78310 LIFESCI
TITLE: Catalytic Mechanism of S-Adenosylhomocysteine Hydrolase: SITE-DIRECTED MUTAGENESIS OF ASP- 130, LYS- 185, ASP-189, AND ASN-190
AUTHOR: Takata, Y.; Yamada, T.; Huang, Y.; Komoto, J.; Gomi, T.; Ogawa, H.; Fujioka, M.; Takusagawa, F.
CORPORATE SOURCE: Department of Molecular Biosciences, University of Kansas, Lawrence, Kansas 66045-7534, USA; E-mail: xraymain@ku.edu
SOURCE: Journal of Biological Chemistry [J. Biol. Chem.], (20020621) vol. 277, no. 25, pp. 22670-22676.
ISSN: 0021-9258.
DOCUMENT TYPE: Journal
FILE SEGMENT: N
LANGUAGE: English
SUMMARY LANGUAGE: English
AB S- ***Adenosylhomocysteine*** ***hydrolase*** (***AdoHcyase***) catalyzes the hydrolysis of S- ***adenosylhomocysteine*** to form adenosine and homocysteine. On the bases of crystal structures of the wild

type enzyme and the D244E ***mutated*** enzyme complexed with 3'-keto-adenosine (D244E super(.)Ado*), we have identified the important amino acid residues, Asp-130, Lys-185, Asp-189, and Asn-190, for the catalytic reaction and have proposed a catalytic mechanism (Komoto, J., Huang, Y., Gomi, T., Ogawa, H., Takata, Y., Fujioka, M., and Takusagawa, F. (2000) J. Biol. Chem. 275, 32147-32156). To confirm the proposed catalytic mechanism, we have made the D130N, K185N, D189N, and N190S ***mutated*** enzymes and ***measured*** the catalytic activities. The catalytic rates (k sub(cat)) of D130N, K185N, D189N, and N190S ***mutated*** enzymes are reduced to 0.7%, 0.5%, 0.1%, and 0.5%, respectively, in comparison with the wild type enzyme, indicating that Asp-130, Lys-185, Asp-189, and Asn-190 are involved in the catalytic reaction. K sub(m) values of the ***mutated*** enzymes are increased significantly, except for the N190S ***mutation*** , suggesting that Asp-130, Lys-185, and Asp-189 participate in the substrate binding. To interpret the kinetic data, the oxidation states of the bound NAD molecules of the wild type and ***mutated*** enzymes were ***measured*** during the catalytic reaction by monitoring the absorbance at 340 nm. The crystal structures of the WT and D244E super(.)Ado*, containing four subunits in the crystallographic asymmetric unit, were re-refined to have the same subunit structures. A detailed catalytic mechanism of ***AdoHcyase*** has been revealed based on the oxidation states of the bound NAD and the re-refined crystal structures of WT and D244E super(.)Ado*. Lys- 185 and Asp-130 abstract hydrogen atoms from 3'-OH and 4'-CH, respectively. Asp-189 removes a proton from Lys-185 and produces the neutral N zeta (-NH sub(2)), and Asn-190 facilitates formation of the neutral Lys-185. His-54 and His-300 hold and polarize a water molecule, which nucleophilically attacks the C5'- of 3'-keto-4',5'-dehydroadenosine to produce 3'-keto-Ado.

L4 ANSWER 25 OF 50 LIFESCI COPYRIGHT 2005 CSA on STN
ACCESSION NUMBER: 97:21163 LIFESCI
TITLE: Chemical modification and site-directed mutagenesis of cysteine residues in human placental S-adenosylhomocysteine hydrolase
AUTHOR: Yuan, Chong-Sheng; Ault-Riche, D.B.; Borchardt, R.T.*
CORPORATE SOURCE: Simons Res. Labs., Dep. Pharma. Chem., Univ. Kansas, 2095 Constant Ave., Lawrence, KS 66047, USA
SOURCE: J. BIOL. CHEM., (1996) vol. 271, no. 45, pp. 28009-28016. ISSN: 0021-9258.
DOCUMENT TYPE: Journal
FILE SEGMENT: N
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Human placental S- ***adenosylhomocysteine*** (AdoHcy) ***hydrolase*** (EC 3.3.1.1) was inactivated by 5',5-dithiobis(2-nitrobenzoic acid) following pseudo-first-order kinetics. Modification of three of the 10 cysteine residues per enzyme subunit resulted in complete inactivation of the enzyme. The three modified cysteine residues were identified as Cys super(113), Cys super(195), and Cys super(421), respectively, by protein sequencing after modification with [1-super(14)C]iodoacetamide. Of the three modifiable cysteines, Cys super(113) and Cys super(195) could be protected from modification in the presence of the substrate adenosine (Ado), which also protected the enzyme from inactivation. On the other hand, Cys super(421) was not protected by Ado, and modification of Cys super(421) alone did not affect the enzyme activity. To verify whether some of these cysteine residues are important for the enzyme catalysis, these three cysteine were replaced by either serine or aspartic acid site-directed mutagenesis. ***Mutants*** of both Cys super(113) (C113S and C113D) and Cys super(421) (C421S and C421D) had enzyme activities similar to that of the wild-type enzyme, and only slight changes were observed in the steady-state kinetics ***measured*** in both the synthetic and hydrolytic directions. However, ***mutants*** of Cys super(195) (C195D and C195S) displayed drastically reduced enzyme activities, and k sub(cat) values were only 7 and 12% of that of the wild-type enzyme, respectively, resulting in a calculated loss in binding energy (Delta Delta G) of approximate 1 Kcal/mol. The Cys super(195) ***mutants*** were capable of catalyzing both the 3'-oxidative and 5'-hydrolytic reactions, as evidenced by the reduction of E times NAD super(+) to NADH and formation of the 5'-hydrolytic product when incubated

with (E)-5',6'-didehydro-6' -deoxy-6'-chlorohomoadenosine at rates comparable with those catalyzed by the wild-type enzyme. However, ***mutations*** of the Cys super(195) severely ***altered*** the 3'-reduction potential as evidenced by the drastic reduction in the rate of [2,8- super(3)H]Ado release from the E super(-NADPH).[2,8-super(3)H]3'-keto-Ado complex. Circular dichroism studies of the Cys super(195) ***mutants*** confirmed that the observed effects are not due to changes in secondary structure. These results suggested that the Cys super(195) is involved in the catalytic center and may play an important role in maintaining the 3'-reduction potential for effective release of the reaction products and regeneration of the active form (NAD super(+) form) of the enzyme; the Cys super(113) is located in or near the substrate binding site, but plays no role beneficial to the catalysis; and the Cys super(421) is a nonessential residue, which also explains why Cys super(421) does not occur in any other known AdoHcy ***hydrolases*** .

L4 ANSWER 26 OF 50 LIFESCI COPYRIGHT 2005 CSA on STN ✓
ACCESSION NUMBER: 94:72596 LIFESCI
TITLE: The mouse lethal nonagouti (a super(x)) mutation deletes the S-adenosylhomocysteine hydrolase (Ahcy) gene
AUTHOR: Miller, M.W.; Duhl, D.M.J.; Winkes, B.M.; Arredondo-Vega, F.; Saxon, P.J.; Wolff, G.L.; Epstein, C.J.; Hershfield, M.S.; Barsh, G.S.*
CORPORATE SOURCE: Dep. Pediatr. and Howard Hughes Med. Inst., Stanford Univ. Sch. Med., Stanford, CA 94305-5428, USA
SOURCE: EMBO J., (1994) vol. 13, no. 8, pp. 1806-1816.
ISSN: 0261-4189.
DOCUMENT TYPE: Journal
FILE SEGMENT: G
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The lethal nonagouti (a super(x)) ***mutation*** is a hypomorphic allele of the agouti coat color locus which, when homozygous, also leads to embryonic death around the time of implantation. To understand the molecular basis of these phenotypes, we identified and cloned a deletion breakpoint junction present in the a super(x) chromosome. Long range restriction mapping demonstrated a simple deletion of similar to 100 kb, which does not affect agouti coding sequences, but begins only 4 kb 3' of the last exon, and thus may affect coat color by removing an agouti 3' enhancer. The Ahcy gene, which codes for the enzyme S-***adenosylhomocysteine*** ***hydrolase*** (***SAHase***), is contained within a 20 kb region within the a super(x) deletion. ***SAHase*** RNA and protein were ***detectable*** in early blastocysts and in embryonic stem cells, respectively, and analysis of embryos derived from an a super(x)/a x a super(x)/a embryo intercross indicated that a super(x)/a embryos die between the late blastocyst and early implantation stages. Treatment of cultured embryos with an ***SAHase*** inhibitor, 3-deaza-aristeromycin, or with metabolites that can result in elevated levels of cellular SAH, resulted in an inhibition of inner cell mass development, suggesting that loss of ***SAHase*** activity in a super(x)/a super(x) embryos is sufficient to explain their death around the time of implantation.

L4 ANSWER 27 OF 50 LIFESCI COPYRIGHT 2005 CSA on STN
ACCESSION NUMBER: 90:83497 LIFESCI
TITLE: Site-directed mutagenesis of rat liver S-adenosylhomocysteinase. Effect of conversion of aspartic acid 244 to glutamic acid on coenzyme binding.
AUTHOR: Gomi, T.; Takata, Y.; Date, T.; Fujioka, M.; Aksamit, R.R.; Backlund, P.S.; Cantoni, G.L.
CORPORATE SOURCE: Dep. Biochem., Toyama Med. and Pharm. Univ., Fac. Med., 2630 Sugitani, Toyama 930-01, Japan
SOURCE: J. BIOL. CHEM., (1990) vol. 265, no. 27, pp. 16102-107.
DOCUMENT TYPE: Journal
FILE SEGMENT: L; N
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Aspartic acid 244 that occurs at the putative NAD super(+) binding site of rat liver S- ***adenosylhomocysteinase*** was replaced by glutamic acid by oligonucleotide-directed mutagenesis. The ***mutant*** enzyme was

purified to homogeneity. In contrast to the wild-type enzyme, which possesses 1 mol of tightly bound NAD super(+) per mol of enzyme subunit, the ***mutant*** enzyme had only 0.05 mol of NAD super(+). The ***mutant*** enzyme, after removal of the bound compounds by acid-ammonium sulfate treatment, exhibited S-***adenosylhomocysteinase*** activity when ***assayed*** in the presence of NAD super(+).

L4 ANSWER 28 OF 50 LIFESCI COPYRIGHT 2005 CSA on STN ✓
ACCESSION NUMBER: 88:3504 LIFESCI
TITLE: SV sub(LM21), a mutant of Sindbis virus able to grow in Aedes albopictus cells in the absence of methionine, shows increased sensitivity to S-adenosylhomocysteine hydrolase inhibitors such as neplanocin A.
AUTHOR: Durbin, R.K.; De Clercq, E.; Stollar, V.
CORPORATE SOURCE: Dep. Mol. Genet. and Microbiol., Univ. Med. and Dent. New Jersey, Robert Wood Johnson Med. Sch., Piscataway, NJ 08854-5635, USA
SOURCE: VIROLOGY., (1988) vol. 163, no. 1, pp. 218-221.
DOCUMENT TYPE: Journal
FILE SEGMENT: V; G
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Inhibition of S-***adenosylhomocysteine*** (AdoHcy) ***hydrolase*** by compounds such as neplanocin A (NPA) leads to the build-up of AdoHcy and the inhibition of methyltransferase enzymes. Whether ***assayed*** by efficiency of plaquing or virus yield, SV sub(LM21), a ***mutant*** of Sindbis virus resistant to methionine deprivation, was more sensitive to NPA than was the standard virus (SV sub(std)) from which it was derived. For example, whereas 10 mu g NPA/ml depressed the yield of SV sub(LM21) by more than 30-fold, the yield of SV sub(std) was not significantly affected. Similar differences in sensitivities were shown to three other compounds which inhibit AdoHcy ***hydrolase*** . These results support the idea that SV sub(LM21) codes for an ***altered*** RNA methyltransferase.
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1	FILE CEN
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626	FILE EMBASE

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          183  FILE ESBIOBASE
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            1  FILE FROSTI
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            2  FILE IMSRESEARCH
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           16  FILE NTIS
            1  FILE OCEAN
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            3  FILE PROMT
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          478  FILE TOXCENTER
          190  FILE USPATFULL
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L3          238 S (MUTANT# OR MUTAT? OR VARIANT? OR ALTER?) (S) L2
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L5           28 DUP REM L4 (22 DUPLICATES REMOVED)

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